REMARKS

Claims 1 and 2 have been combined with editorial amendment to make the meaning clearer as regards prevention, and claims 2-3, 11-13 and 15 have been deleted.

The dependency of claims 14 and 16 has been amended in response to the objection under 35 USC 112. These claims are now dependent on claim 1 and refer to the administration of a bombesin receptor antagonist together with specific other compounds or a specific class of compounds, the reference to "vasodilator" being removed.

The dependency of claim 21 has been amended consequentially on the cancellation of claim 11.

Claims 24-36 are newly introduced and relate to features of the treatment of sexual dysfunction in females. Claims 37-46 are also newly introduced and relate to aspects of the treatment of sexual dysfunction in males. Support for claims 29-36 is at page 48 line 22 – page 49 line 29.

Support for claims 24-27 is at page 5 lines 30-33. Support for claim 28 is at page 3 lines 4-5 when read with the definition of sexual dysfunction at page 1 lines 11-19. Support for claims 29-36 is at page 48 line 22 – page 49 line 29. Support for claims 37 and 38 is at page 3 line 8 and support for claim 39 is at page 6 line 31. Support for claims 40-46 is at page 48 line 22 – page 49 line 29.

The Examiner has objected to claim 1 as anticipated by *Howell et al WO98/07718*. Claim 1 of the subject application relates to a method of treating or preventing sexual dysfunction, which comprises administering to a subject suffering from and in need of treatment an effective amount of a bombesin receptor antagonist. *Howell et al* disclose a class of compounds said to be effective in treating or

preventing depression, psychoses, seasonal affective disorders, cancer, feeding disorders, gastrointestinal disorders, inflammatory bowel disease, sleep disorders and memory impairment. The objection of anticipation is based on an alleged link between the treatment of depression and the treatment of sexual dysfunction. However, this link does not exist for the reasons set out below:

- Many patients who suffer from depression do not suffer from sexual dysfunction. Correspondingly many patients who suffer from sexual dysfunction do not suffer from depression.
- It does not follow that a medicament that is useful for the treatment of depression will inherently and inevitably have a positive effect on the sexual function of the patient. Many anti-depressants cause sexual dysfunction when administered to patients who are not suffering from sexual dysfunction. For example, tricyclic antidepressants have side effects including decreased libido, erectile dysfunction, impotence, delayed or absent ejaculation, inhibited orgasm and anorgasmia. Monoamine oxidase inhibitors have been reported as having similar side effects as also have selective serotonin reuptake inhibitors (SSRIs). For example, a data-sheet for the SSRI Prozac which is available on-line at http://www.inhousepharmacy.co.uk/anti-depressants/prozac.html and is described as "perhaps the most well-known of all the anti-depressants" contains the following warning:

  "A lowered sex drive is also a common side effect of this, as with most antidepressants. If you experience any unusual symptoms or are concerned about side effects in any way, it is important that you discuss this with your doctor or consult a pharmacist for advice..."

It is therefore submitted that the features of claim 1 are not met by the disclosure of *Howell et al* which contains no teaching, either express or implicit, concerning the treatment of sexual dysfunction. Reconsideration and withdrawal of the objection under 35 USC 102 against the subject matter of claim 1 is requested.

The Examiner has further objected that the subject matter of claim 5, which concerns the treatment of sexual dysfunction in the human female, lacks novelty having regard to the disclosure of *Howell et al.* However, the feature of claim 5 is not met by that reference which is silent about the treatment of human females for sexual dysfunction. Reconsideration and withdrawal of the objection under 35 USC 102 against the subject matter of claim 5 is therefore requested.

The Examiner has objected under 35 USC 103(s) that the subject matter of claims 1-23 is unpatentable over the disclosures of *Howell et al* and *Hurel et al* in view of the *Merck manual* and *sildenafil* prescribing information. The applicants aver that bombesin receptor antagonists treat sexual dysfunction, whether in males or in females, by a mechanism that has no nexus with the treatment of depression and no nexus with vasodilation by inhibiting PDE5 or otherwise, and that the ability of bombesin receptor antagonists to treat sexual dysfunction is not disclosed or suggested by any of the references relied on by the Examiner.

Howell et al is relied on as teaching a method of treating or preventing depression, but for the reasons noted above, this does not amount to a disclosure of treating sexual dysfunction. Since many antidepressants have an adverse effect on sexual function, a disclosure that a group of compounds is effective for the treatment of depression does not disclose or suggest that they would be effective for the treatment of sexual dysfunction.

Hurel et al is relied on as providing a teaching that bombesin-like peptide antagonists have vasoactive properties. However, study of that document reveals that it does not provide basis for a general teaching that bombesin-like peptide antagonists have vasoactive properties or act as systemic vasodilators. The authors were concerned with patients suffering from pulmonary hypertension (high blood pressure in the lungs), which is a relatively rare condition. It is usually associated with congestive heart failure or chronic obstructive lung disease, but in the case of so-

called "primary pulmonary hypertension" it has no known cause and is difficult to treat. *Hurel et al* postulated that the bombesin-like peptide GRP has vasoactive properties within the innermost layer of the pulmonary artery (pulmonary endothelium) and that a GRP antagonist might have a beneficial effect. They therefore infused BIM26226, which is a polypeptide and is a bombesin receptor antagonist, through a catheter into the pulmonary artery. They observed a fall in pulmonary systolic and diastolic blood pressure, but they were uncertain about the mechanism for the observed effect and, as is apparent from the figures, in the table there was a rise in systemic blood pressure. It is therefore apparent that the blood pressure reducing effect observed by *Hurel et al* was local to the pulmonary artery and that BIM26226 is not a peripheral vasodilator. The *Hurel et al* work is further described in the corresponding Hurel *WO 96/28214* and *US 5650395*, copies of which accompany this response and are made of record. The Examiner will note that *Hurel* refers in 5650395 at column 1 line 36 onwards to an autonomous endocrine system within the lungs termed the pulmonary neuroendocrine system that had been shown to secrete gastrin-related peptide, and claims the use of a bombesin antagonist *only* in relation to the medical indication of lowering pulmonary systolic pressure. Thus claim 1 of the issued US patent reads:

> "A method of lowering the pulmonary systolic pressure of a subject suffering from pulmonary hypertension, said method comprising administering to the subject an amount of a bombesin antagonist, said amount being effective to lower the systolic pressure."

The applicants submit that the present disclosure supports a claim of similar scope for the surprising novel indication of treating sexual dysfunction.

Even if *Hurel et al* had provided a general teaching of vasoactive properties as alleged by the Examiner, that would not lead the skilled person to conclude that the disclosed compound might be used in the treatment of sexual dysfunction. Antihypertensive medications may cause erectile dysfunction either by drug-specific

effects or by decreasing the systolic pressure and thereby decreasing the intracavernosal penile pressure. This result is especially prevalent in patients with diabetes or hypertension who have an underlying microvascular disease. The *Merck Manual of Geriatrics* comments in Chapter 115, Sexual Dysfunction in Men (http://www.merck.com/pubs/mm_geriatrics/sec14/ch115.htm):

> "About 25% of cases of erectile dysfunction are caused by drugs ... especially antihypertensives (most notably reserpine, β-blockers, guanethidine, and methyldopa) ..."

As a further example, benzazepril (Captopril), which is an ACE inhibitor used for the treatment of high blood pressure and congestive heart failure, may give rise in men to reduced libido and more rarely impotence (see http://www.healthcentral.com/mhc/top/001803.cfm).

The applicants are not aware of any reason why a bombesin receptor antagonist should act as a vasodilator, and they are aware of no other report of bombesin receptor antagonists acting as vasodilators. Furthermore, they believe that bombesin receptor antagonists treat sexual dysfunction not by acting as vasodilators but instead by acting on bombesin receptors, and especially BB1 receptors, in the brain. This belief is supported by the reported existence of BB1 receptors in the ventromedial hypothalamus and by the experiment reported in Example 4 of this application, which shows that intracerebroventricular administration of a bombesin receptor antagonist to a female rat produces a dose-dependent increase in the percentage of time spent investigating a male stimulus. *Hurel et al* concluded that bombesin-like peptide (BLP) antagonists could have a role in the treatment of primary pulmonary hypertension, but there is no mention of bombesin receptors within the brain, no disclosure that bombesin receptor antagonists could have any effect on sexual function and nothing to suggest that bombesin receptor antagonists could be useful for the treatment of sexual dysfunction.

The *Merck manual* discloses that depression is a cause of sexual dysfunction in both the male and the female, but, as noted above, the converse is not true and many antidepressants lower rather than improve sexual function.

The mechanism of erection in the male is now well known. Nitric oxide released in the corpus cavernosum is converted to cGMP, which causes muscle relaxation. cGMP is removed by an enzyme called PDE5, and *sildenafil* achieves its effect on erectile dysfunction by selectively inhibiting that enzyme. There is nothing in the cited data sheet for *sildenafil* to suggest that an inhibitor of bombesin-like peptides (which binds not to an enzyme but instead to a membrane-bound protein which is a G-protein coupled receptor) could treat sexual dysfunction.

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time when the invention was made to use a bombesin-like peptide antagonist (i.e. start from the disclosure of *Hurel et al*) and/or a non-peptide bombesin antagonist (i.e. start from *Howell et al*) in a method of treating sexual dysfunction. One starting point, *Hurel et al*, for the reasons explained above has no relevance to sexual dysfunction because it discloses only an effect local to the pulmonary artery, and contains information from which it is apparent that the compound used is not a peripheral vasodilator. The other postulated starting point, *Howell et al*, does not suggest a method of treating sexual dysfunction because the postulated link between treating depression and treating sexual dysfunction does not exist.

As regards motivation, a disclosure that a compound is effective for the treatment of depression would not motivate a skilled person to investigate the treatment of sexual dysfunction for the reasons indicated above. The Examiner further suggests that bombesin receptor antagonists are vasodilators analogous to *sildenafil*, but as explained above the reference relied on by the Examiner does not disclose a vasodilator. Bombesin receptor antagonists were known to bind to G-coupled receptor proteins that are membrane bound and are involved in cell

receptor antagonist. It is therefore submitted that the subject matter of claim 25 is free from objection under 35 USC 103.

Claim 26 specifies that the sexual dysfunction is female orgasmic disorder or anorgasmy. At present there is no drug treatment. None of the references individually or in combination teaches or suggests that female orgasmic disorder or anorgasmy can be treated by administration of a bombesin receptor antagonist. It is therefore submitted that the subject matter of claim 26 is free from objection under 35 USC 103.

Claim 27 specifies that the sexual dysfunction is female sexual pain disorder. Treatment where the pain arises because of atrophic vaginitis is by oral or transdermal oestrogen therapy. None of the references individually or in combination teaches or suggests that female sexual pain disorder can be treated by administration of a bombesin receptor antagonist. It is therefore submitted that the subject matter of claim 27 is free from objection under 35 USC 103.

Claim 28 specifies that the sexual dysfunction occurs in a female receiving an antidepressant or an antihypertensive. None of the references individually or in combination teaches or suggests that females suffering from a sexual dysfunction arising from treatment with an antidepressant or antihypertensive can be treated by administration of a bombesin receptor antagonist. It is therefore submitted that the subject matter of claim 28 is free from objection under 35 USC 103.

Claim 37 specifies that the sexual dysfunction is male erectile dysfunction. Currently this condition can be treated by sildenafil given orally or by prostaglandin E1 given by intraeurethral pellet or intercavernosal injection. None of the references individually or in combination teaches or suggests that males suffering from erectile dysfunction can be treated by administration of a bombesin receptor antagonist. The mechanism by which a bombesin receptor antagonist treats male erectile dysfunction is believed to involve BB1 receptors in the brain (CNS potentiation of the descending

neuronal pathways that control penile erection), whereas the existing treatments act directly on cavernosal blood flow. It is therefore submitted that the subject matter of claim 37 is free from objection under 35 USC 103.

Claim 38 specifies that the sexual dysfunction is a male psychogenic dysfunction. None of the references individually or in combination teaches or suggests that males suffering from psychogenic sexual dysfunction can be treated by administration of a bombesin receptor antagonist. The mechanism by which a bombesin receptor antagonist treats psychogenic sexual dysfunction is believed to involve BB1 receptors in the brain, and in this respect is believed to be unique. It is therefore submitted that the subject matter of claim 38 is free from objection under 35 USC 103.

Claim 39 specifies that the sexual dysfunction is a male drug-induced sexual dysfunction. None of the references individually or in combination teaches or suggests that males suffering from a sexual dysfunction arising from this cause can be treated by administration of a bombesin receptor antagonist. It is therefore submitted that the subject matter of claim 39 is free from objection under 35 USC 103.

A number of the claims not previously discussed relate to combination therapy.

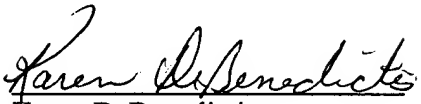
Claim 29 specifies that the bombesin receptor antagonist should be administered to a female subject in combination with a vasodilator that acts on local blood flow at the clitoris or vagina or on lubricant secretion. Claim 30 specifies for female subjects that a component of the combination should be a PDE 5 inhibitor and claim 31 specifies, again for female subjects, that that component should be sildenafil or a pharmaceutically acceptable salt thereof. Claim 40 specifies for male subjects that the bombesin receptor antagonist should be administered in combination with a vasodilator that acts on local blood flow to the penis. Claim 41 specifies for male

subjects that a component of the combination should be a PDE 5 inhibitor and claim 42 specifies, again for male subjects, that that component should be sildenafil or a pharmaceutically acceptable salt thereof. Each of these claims relates to the combination of firstly a bombesin receptor antagonist whose mode of action involves BB1 receptors in the brain (CNS potentiation of the descending neuronal pathways that control penile erection), and secondly a vasodilator which acts directly on blood flow to the genitalia. This combination of features is not disclosed or suggested in any of the cited references. An experiment carried out by the applicants administering to male rats as bombesin receptor antagonist the compound (2*S*)-*N*-{[1-(4-aminophenyl)cyclohexyl]methyl}-3-(1*H*-indol-3-yl)-2-methyl-2-{[(4-nitroanilino)carbonyl]amino}propanamide in combination with a PDE5 inhibitor which is the compound (3-ethyl-5-{5-[4-ethylpiperzino)sulphonyl-2-propoxyphenyl}-2-(2-pyridylmethyl)-6,7-dihydro-2H-pyrazolo[4,3-*d*]pyrimidin-7-one; see WO98/491066) produced a marked increase in intracavernosal pressure compared to what was achievable with the same dose of the bombesin receptor antagonist alone. BB1 antagonists and PDE5 inhibitors or combinations of the two, have no significant effect on un-stimulated intracavernosal pressure i.e. they do not induce an increase in the absence of sexual drive/arousal. This data illustrates that there are clinical benefits of concomitant administration of a PDE5 inhibitor and a bombesin antagonist over PDE5 inhibitor therapy alone. These benefits include increased efficacy and opportunities to treat MED subgroups that do not respond to PDE5 inhibitor therapy. It is therefore submitted that the subject matter of claims 29-31 and 40-42 is free from objection under 35 USC 103.

Claims 14 and 16-23 relate to further aspects of combination therapy for males and females. Claims 32-36 disclose features of combination therapy for the human female and claims 43-46 disclose features of combination therapy for the human male. These claims are allowable *inter alia* because they are each dependent on an allowable base claim.

In view of the above amendments, and remarks, applicants maintain that Claims 1-46 are in condition for allowance.

Respectfully submitted,



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CLAIMS

1. A method of treating or preventing sexual dysfunction which comprises administering to a subject suffering or liable to suffer therefrom and in need of treatment or prevention an effective amount of a bombesin receptor antagonist.

~~2. A method of preventing sexual dysfunction which comprises administering to a subject suffering therefrom and in need of treatment an effective amount of a bombesin receptor antagonist.~~

~~3. The method of claim 1, wherein the dysfunction is associated with hypoactive sexual desire disorders, sexual arousal disorders, orgasmic disorders or anorgasmy, or sexual pain disorders.~~

4. The method of claim 1, wherein the dysfunction is associated with generalised unresponsiveness and ageing-related decline in sexual arousability or with drug–induced sexual dysfunction.

5. The method of claim 1, wherein the subject is a human female.

6. The method of claim 1, wherein the subject is a human male.

7. The method of claim 1, wherein the bombesin receptor antagonist has a preferential affinity for the BB_1 receptor.

8. The method of claim 1, wherein there is administered to the subject an effective amount of a non-peptide bombesin receptor antagonist.

9. The method of claim 8, wherein the non-peptide bombesin receptor antagonist is a compound that is absorbable when administered orally.

10. The method of claim 1, wherein there is administered to the subject an effective amount of a bombesin receptor antagonist which is a peptide.

~~11. The method of claim 1, which comprises administering to a subject a bombesin receptor antagonist in combination with a vasodilator useful for the treatment of sexual dysfunction.~~

~~12. The method of claim 22, wherein the vasodilator is a PDE5 inhibitor.~~

~~13. The method according to claim 23 wherein the PDE5 inhibitor is sildenafil or a pharmaceutically acceptable salt thereof.~~

14. The method of claim ~~22~~ *1*, wherein ~~the vasodilator is~~ the bombesin receptor antagonist is administered in combination with ~~selected from~~ alprostadil or phentolamine.

~~15. The method of claim 22, wherein the vasodilator is a VIP enhancer.~~

16. The method of claim ~~22~~ *1*, wherein the bombesin receptor antagonist is administered in combination with ~~the vasodilator is~~ a compound that promotes production of NO.

17. The method of claim 1, which comprises administering to a subject a bombesin receptor antagonist in combination with a modulator of steroid hormones, a steroid hormone or a hormone product useful for the treatment of sexual dysfunction.

18. The method of claim 17, wherein the steroid hormone is selected from oestrogens or androgens.

19. The method of claim 1, which comprises administering to a subject a bombesin receptor antagonist in combination with a neurotransmitter agonist or antagonist, a monoamine synthesis modifier, or a monoamine metabolism or uptake modifier useful for the treatment of sexual dysfunction.

20. The method of claim 19, wherein the neurotransmitter agonist or antagonist is selected from quinelorane, ritanserin, para-chlorophenylalanine or imipramine.

21. The method of claim ~~11~~ *1*, wherein the bombesin receptor antagonist and ~~the~~ a vasodilator are simultaneously administered to the subject in the form of a composition containing a unit dose of the bombesin receptor antagonist, a unit dose of the vasodilator and a pharmaceutically acceptable carrier or diluent.

22. The method of claim 17 wherein the bombesin receptor antagonist and the modulator of steroid hormones, steroid hormone or hormone product are simultaneously administered to the subject in the form of a composition containing a unit dose of the bombesin receptor antagonist, a unit dose of the modulator of steroid hormones, steroid hormone or hormone product and a pharmaceutically acceptable carrier or diluent.

23. The method of claim 19 wherein the bombesin receptor antagonist and the neurotransmitter agonist or antagonist, monoamine synthesis modifier, or monoamine metabolism or uptake modifier are simultaneously administered to the subject in the form of a composition containing a unit dose of the bombesin receptor antagonist, a unit dose of the neurotransmitter agonist or antagonist, monoamine synthesis modifier, or monoamine metabolism or uptake modifier and a pharmaceutically acceptable carrier or diluent.

24. The method of claim 5, wherein the sexual dysfunction is hypoactive sexual desire disorder.

25. The method of claim 5, wherein the sexual dysfunction is a sexual arousal disorder.

26. The method of claim 5, wherein the sexual dysfunction is an orgasmic disorder or anorgasmy.

27. The method of claim 5, wherein the sexual dysfunction is sexual pain disorder.

28. The method of claim 5, wherein the subject is receiving an antidepressant or antihypertensive.

29. The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with a vasodilator which acts on local blood flow at the clitoris or vagina or on lubricant secretion.

30. The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with a PDE5 inhibitor.

31. The method of claim 30, wherein the PDE5 inhibitor is sildenafil or a pharmaceutically acceptable salt thereof.

32. The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with a VIP enhancer.

33. The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with an angiotensin-2 receptor.

34. The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with an oestrogen.

35. The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with an androgen.

36. The method of claim 5, wherein the bombesin receptor antagonist is administered to the subject in combination with a neurotransmitter modulator.

37. The method of claim 6, wherein the sexual dysfunction is erectile dysfunction.

38. The method of claim 6, wherein the sexual dysfunction is psychogenic.

39. The method of claim 6, wherein the sexual dysfunction is drug-induced.

40. The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with a vasodilator which acts on local blood flow at the penis.

41. The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with a PDE5 inhibitor.

42. The method of claim 6, wherein the PDE5 inhibitor is sildenafil or a pharmaceutically acceptable salt thereof.

43. The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with a VIP enhancer.

44. The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with an angiotensin-2 receptor.

45. The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with an androgen.

46. The method of claim 6, wherein the bombesin receptor antagonist is administered to the subject in combination with a neurotransmitter modulator.